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Hemostasis and thrombosis in extreme physiological and pathological conditions

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The hemostatic system is responsible for limiting blood loss upon vascular injury, and is designed to rapidly react to breaches in the endothelial cell lining. Components of this system are subject to powerful regulatory mechanisms including various antihemostatic actions of the endothelium, antihemostatic actions from proteins in plasma, and blood flow that removes activated hemostatic proteins from the growing thrombus. A well-orchestrated balance between pro- and anti-hemostatic forces ensures hemostatic balance and avoids spontaneous bleeding or thrombotic episodes. It is evident that hemostatic balance is crucial to avoid these complications as evidenced by the pathology associated with a deficiency of pro- or anti-coagulant proteins (e.g., severe and spontaneous bleeding in hemophilia and substantially elevated thrombotic risk in patients with deficiencies in some of the natural anticoagulants). While congenital or acquired disorders may alter multiple components of the hemostatic system simultaneously, such complex changes in the hemostatic system may not necessarily lead to severe pathology. For example, the complex hemostatic changes in patients with liver disease leads to a hemostatic rebalance without a clinical phenotype in many patients, which demonstrates the resilience of the hemostatic system (1). Likewise, hemostatic challenges resulting from surgery or trauma are not necessarily related to a dismal hemostatic outcome (2,3). In this issue of *Seminars of Thrombosis and Hemostasis*, we explored consequences of remarkable physiological or pathological conditions on the hemostatic system. As we will see, some 'extreme' conditions may be without clinical consequences, while others are related to a substantial risk of bleeding or thrombosis. Moreover, a remarkable set of challenges to the hemostatic system, i.e., hemostatic activators or inhibitors in a variety of venoms, are potentially useful as therapeutic agents.

We will start this issue by discussing effects of physiological extremes. First, Kenet and coworkers (4) discuss the hemostatic system in the very young. It is well known that the hemostatic system in newborns and very young children has a remarkably different composition than that in adults, with decreased plasma levels of most of the activators and inhibitors. Despite these differences, most children fortunately do well and are in excellent hemostatic balance. The paper by Kenet discusses those rare cases in which young children suffer from bleeding or thrombotic complications in the context of the concept of developmental hemostasis. Next, Tzoran and coworkers (5) discuss the hemostatic changes that occur as a consequence of ageing. As in the very young, the hemostatic system in the oldest old is substantially different from younger adults. However, in this population, the risk of thrombotic disease increases tremendously, and interactions with chronic illnesses are associated with important thrombotic issues. The subsequent 'extreme condition' is discussed by Hunt (6), who addresses hemostatic changes in extremes of body weight. Very low body weight is associated with incompletely characterized hemostatic changes, which include decreased blood cell counts and platelet hyperaggregability. Among the many clinical consequences of severe obesity is a hypercoagulable state that is related to an increased risk of venous and arterial thrombosis. The author also discusses mechanisms and clinical consequences of the hemostatic changes associated with (severe) obesity. The next paper by Kicken and coworkers (7) deals with extreme exertion. The authors propose that a hypercoagulable state induced by strenuous exercise is balanced by a concomitant development of a hyperfibrinolytic state. However, this compensatory mechanism largely disappears during recovery, which may be important in the context of an increased risk of cardiovascular events in athletes.

The next section in this issue discusses hemostatic challenges caused by disease. Levi (8) discusses effects of abnormal body temperature on the hemostatic system. Heatstroke is used to provide an example of hemostatic changes that may occur as a result of hyperthermia. Heatstroke may lead to disseminated intravascular coagulation which may contribute to a dismal outcome. Hypothermia may

occur in conditions like trauma or imposed intentionally in order to protect the brain in patients that have had a cardiac arrest or acute liver failure. Although hemostatic changes do occur, the clinical consequences may be limited. Hoirisch-Clapauch (9) then discusses the risks of bleeding and thrombosis related to anxiety. The author puts forward the thought-provoking hypothesis that anxiety combined with hypofibrinolytic states (defined as severe depression or a high-carbohydrate, low-protein, low-fiber diet and a sedentary lifestyle) has a role in the pathogenesis of thrombotic events, and that part of these events, currently classified as unprovoked, are in reality provoked by high anxiety states. The next paper by Jacob and coworkers (10) deals with the effects of stress on the hemostatic system and concludes that the hypercoagulable state induced by stress could be related to a combination of neurotransmitters and hormones and the effects of stress on hemodynamics. Vadasz and Toubi (11) then discuss the hemostatic changes in allergy, specifically in asthma and chronic spontaneous urticaria. The authors show complex hemostatic changes in both disorders and demonstrate that these changes are, at least partly, related to the effects of the immune system on hemostasis. Subsequently Elbers and coworkers (12) discuss the interplay between thyroid hormones and hemostasis, showing that hypothyroidism is associated with hypocoagulability and risk of bleeding, and hyperthyroidism with hypercoagulability and risk of venous thrombosis. In addition, the paper describes effects of malignant thyroid disease on developing venous thrombosis, which relates to local stasis of the blood due to compression effects of the expanding tumor. The next paper by Putri and coworkers (13) discusses thrombocytopenia and platelet function defects that are frequent complications of tropical diseases such as malaria and Dengue fever. Interestingly, in some tropical diseases in which patients commonly develop thrombocytopenia bleeding is rare (e.g. in malaria), whether in other diseases bleeding is an important complication of the disease, which may be related to preservation of platelet function in malaria. The paper therefore discusses mechanisms and clinical consequences of thrombocytopenia and platelet function defects in tropical diseases and highlights the difficulties in studying platelet properties in resource-poor countries where these such diseases are frequent. A final contribution by Koh and coworkers (14) gives an extensive overview of proteins and peptides isolated from different types of venom that interfere with a variety of hemostatic processes. The paper also gives an overview on discovery and development of venom-derived antiplatelet, anticoagulant, and thrombolytic agents. Venom-derived compounds are not only used in diagnostic assays of hemostasis (e.g., ristocetin-induced platelet agglutination or the Russel Viper Venom time), but have clear potential as pharmacological agents (e.g., hirudin).

Taken together, the papers in this issue of the journal highlight subtle or pronounced hemostatic effects of a wide variety of physiological or pathological extremes. The clinical consequences associated with hemostatic alterations by these extremes may teach us valuable lessons around the requirements for hemostatic balance in health and disease. In addition, these reviews accentuate the variety of triggers that may alter the hemostatic system, and stress links between physiological or pathological conditions and hemostasis that may not be immediately apparent. We sincerely hope you enjoy reading the wide range of papers assembled in this issue.

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